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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/806,419	03/23/2004	Adonia E. Papathanassiu	A8448-1	2824

7590 07/14/2006

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EXAMINER	
YAEN, CHRISTOPHER H	
ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 07/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/806,419	PAPATHANASSIU, ADONIA E.	
	Examiner	Art Unit	
	Christopher H. Yaen	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *1-6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 March 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *exhibits 1 and 2*.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of group II (claims 7-20) in the reply filed on 4/21/2006 is acknowledged.

2. Claims 1-20 are pending, claims 1-6 are withdrawn from further consideration as being drawn to non-elected subject matter.

3. Claims 7-20 are examined on the merits.

Specification

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. Specifically, the application recites peptide sequence or amino acid sequences which have not been associated with a sequence identification number or SEQ ID No. (see pages 6 and 7 for example). Applicant is required to amend the specification and or the sequence listing to comply with the rules set forth under 37 CFR 1.821-1.825. Failure to comply with the rules under 37 CFR 1.821-1.825 in response to this office action may result in abandonment of the case. The requirement for will not be held in abeyance. Note: the specification has not be reviewed to the extent such that all occurances of non-compliant sequences have been found or noted. Applicant is advised to carefully review the specification for any other non-compliant sequences under 37 CFR 1.821-1.825.

Priority

5. The instant application claims priority to 09/935,145, of which the instant application is a continuation-in-part. The earlier filed application (i.e. 09/935,145) fails to support an antibody which is encoded by either SEQ ID No: 8 or 9 as well as sequence which are at least 95% identical to each of the claimed sequences. Moreover, the earlier filed application fails to support specific species of antibody fragments such as ScFv, diabodies, and triabodies as claimed. Therefore, the filing date of the instant application (i.e. 3/23/2004) will be used for the determination of any earlier prior art. Applicant is invited to point to specific support in any of the earlier filed applications.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 7-17 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 7-17 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 7-17 as written, do not sufficiently distinguish over antibodies as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*,

447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated". See MPEP 2105.

Claim Rejections - 35 USC § 112, 2nd paragraph

7. Claims 7-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 7-12, recites the limitation "said heavy chain" or "said light chain". There is insufficient antecedent basis for this limitation in the claims because the claims only describes an antibody and fails to recite "heavy chain" or "light chain".

Claim Rejections - 35 USC § 112, 1st paragraph

9. Claims 18-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or

absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a pharmaceutical composition comprising an antibody or antibody fragment that binds to SEQ ID No: 4, wherein the antibody is encoded by a nucleic acid sequence which is 95% or 100% identical to SEQ ID No: 8 and 9. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims encompass antibodies which are intended for in vivo use or for therapeutics.

Quantity of experimentation

The quantity of experimentation is deemed high give the lack of guidance in the specification and the general unpredictable nature of using antibodies in vivo for the purposes of treating a subject.

The unpredictability of the art and the state of the prior art

Zetter (Annu. Rev. Med., 1998, v49. Pp. 407-24) teaches that anti-angiogenic treatment can reduce a tumor mass back to its avascular size, but it may not completely eliminate tumors that regress to sizes no longer dependent on increased vascularity (page 417, 2nd column, last paragraph). Thus, the potential for in-vivo micrometastasis is not eliminated. Also, the current state of the art on the latest in-vivo testing of anti-

angiogenic drugs have been mixed. For example, it was recently revealed that the drug Endostatin is unlikely to be the kind of across-the-board cancer cure that many had hoped for. Out of the 61 terminally ill patients tested, not one recovery had been seen (MSNBC News Services, "Mixed results on new cancer drug", November 9, 2000). Hence, it would not be predictable that a pharmaceutical composition intended for the treatment of angiogenesis would be effective in a patient suffering from cancer or in any other angiogenic related disease. Further, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. All of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy. Thus, despite evidence that interaction between the SP-1 ligand and its receptor promotes angiogenesis, the specification offers no guidance and or objective evidence that "inhibiting" this interaction in a patient would effectively inhibit angiogenesis.

Aside from the general unpredictable nature angiogenesis and cancer treatment, the use of antibodies for treatment in general is unpredictable. Jain (Scientific American

July 1994), discloses barriers to the delivery of drugs into solid tumors. These impediments include (1) Non-uniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1); (4) Convection is a necessary mechanism by which larger therapeutics molecules such as antibodies, reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than ½ centimeter in diameter, page 62 col. 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3) and (4) Molecules as large as antibodies (i.e., MW=150,000) would require several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2). Further, in the late 80's, Dillman (Annals of Internal Medicine, Volume 111, pages 592-603, 1989) summarized (see abstract) the status of in-vivo use of monoclonal antibodies for treating cancer wherein despite advances in biotechnology, many major hurdles persist including tumor cell heterogeneity, lack of cytotoxicity, and the development of human anti-mouse antibodies (HAMA). More recently, Weiner (Seminars Oncology, Vol. 26, No.4, 1999, pages 41-50) provided an overview of monoclonal antibody of therapy including some promising activity, however major obstacles to clinical efficacy still exist extending the

unpredictability of this treatment. This includes impaired distribution and delivery of antibody to the tumor site, inadequate trafficking of potential cellular effectors to tumor, antigenic heterogeneity, shed or internalized targets, insufficient target specificity, and induction of HAMA (page 43). Lack of working examples is given added weight in cases involving an unpredictable and undeveloped art such as the treatment of cancer with antibodies. In the instant case, the claims are so broadly drawn, the guidance is so limited, and the art is so unpredictable that it would require undue experimentation to successfully practice the invention as claimed.

Working examples

Lack of working examples is given added weight in cases involving an unpredictable and undeveloped art such as the treatment of cancer with antibodies. In the instant case, the claims are broadly drawn to using the antibody in vivo, the guidance is so limited, and the art is so unpredictable that it would require undue experimentation to successfully practice the invention as claimed. The instant specification fails to provide one of skill in the art with the prerequisite guidance for using the claimed composition in vivo.

Guidance in the specification

The specification provide those of skill in the art with guidance for screening and identifying the heavy and light chains of a particular antibody but fail to show those of skill in the art how to use the claimed invention for in vivo purposes as intended.

Level of skill in the art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that ad, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 112, 1st paragraph

10. Claims 7-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody or "antigen-binding" fragment thereof, or a composition comprising said antibody or antigen binding fragment thereof comprising an amino acid sequence encoded by the nucleic acid sequence of SEQ ID No: 8 or 9, does not reasonably provide enablement for an antibody or antibody binding fragment thereof or a pharmaceutical composition comprising said antibody or antibody binding fragment thereof comprising an amino acid sequence encoded by a nucleic acid sequence which is 95% identical to SEQ ID No: 8 or 9. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to an antibody or antibody-binding fragment, and to a pharmaceutical composition comprising said antibody or antibody-binding fragment thereof wherein the antibody comprises an amino acid sequence which is 95% identical to SEQ ID No: 8 and or 9. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims encompass antibodies which are variants of the antibodies encoded by nucleic acids of SEQ ID No: 8 and or 9.

Quantity of experimentation

The quantity of experimentation in this area is deemed high given the general nature of antibodies binding affinities and the lack of working examples provided in the instant specification.

The unpredictability of the art and the state of the prior art

It is well established in the art that the formation of an intact "antigen-binding" site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibodies which are encoded by nucleic acid sequence which are 95% identical to that of SEQ ID No: 8 and/or 9 will be capable of maintaining the same antigen specificity as those antibodies which are encoded by SEQ ID No: 8 and or 9. Such "variants" (i.e. those which are encoded by sequences which are 95% identical) encompass modifications (e.g. point mutations or substitutions of multiple amino acids) to the CDR regions from the heavy and light chain variable regions of the claimed antibody.

Panka et al (Proc Natl Acad Sci USA Vol 85 3080-3084 5/88) demonstrate that a single amino acid substitution of serine for alanine results in decreased affinity. In at least one case it is well known that an amino acid residue in the framework region is involved in antigen binding (Amit et al Science Vol 233 747-753 1986).

Further, an "antibody-binding fragment" can be any portion of the antibody including any one of the constant regions (CH1-3) and also may be the hinge region. However, the language also reads on small amino acid sequences which are incomplete regions of the constant region of the antibody. There is no support in the specification for linking the variable region to any or all of the myriad "fragments" which are encompassed within this language. One of skill in the art would neither expect nor predict the appropriate functioning of the antibody as broadly as is claimed. It is suggested that applicant amend antibody binding region to antigen binding fragment in order to obviate this rejection.

Working examples

The specification provides little guidance for antibody variants and or antibodies which are encoded by sequence which are 95% identical to SEQ ID No: 8 and/or 9.

Guidance in the specification

The specification provides those of skill in the art with guidance in terms of how to determine the sequence (i.e. identification of the sequence) of the VH and VL regions of an antibody, however, the specification fails to teach those of skill in the art how to make and use antibodies that are encoded by sequences which are 95% identical to SEQ ID No: 8 and/or 9 and at the same time maintain specificity to SEQ ID No: 4.

Level of skill in the art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that ad, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 7-8,13, and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Bigner D. *et al* (WO/9421294A1). The claims recite an antibody or antibody-binding fragment wherein the heavy chain comprises "an amino acid sequence" having 95% or 100% sequence identity to amino acid 1-378 of SEQ ID No: 8. The specification of the instant application defines the term "an" as being "one or more" (see page 10, for

example). As such, "an amino acid" reads on a sequence comprising as little as two amino acids in common with SEQ ID No: 8.

Bigner D. *et al* teach an antibody and a pharmaceutical composition comprising said antibody (see page 10, for example), wherein the antibody comprises "an amino acid sequence" that is at least 95%-100% identical to amino acid 1-378 of SEQ ID No: 8 (see attached sequence alignment - Exhibit 1). The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

13. Claims 9-10, 14, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Barsomian *et al* (WO/9515982A2). The claims recite an antibody or antibody-binding fragment wherein the heavy chain comprises "an amino acid sequence" having 95% or 100% sequence identity to amino acid 1-378 of SEQ ID No: 8. The specification of the instant application defines the term "an" as being "one or more" (see page 10, for example). As such, "an amino acid" reads on a sequence comprising as little as two amino acids in common with SEQ ID No: 9.

Barsomian *et al* teach an antibody, antibody fragments (e.g. ScFv, see page 6, for example), and pharmaceutical compositions comprising "an amino acid sequence"

having at least 95% -100% sequence identity to amino acid 1-372 of SEQ ID No: 9 (see attached sequence alignment - Exhibit 2). The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H. Yaen whose telephone number is 571-272-0838. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christopher Yaen
Art Unit 1643
July 6, 2006

CHRISTOPHER H. YAEN
PRIMARY EXAMINER

Exhibit 2
1 of 2

AAQ92503
ID AAQ92503 standard; cDNA; 723 BP.
XX
AC AAQ92503;
XX
DT 07-FEB-1996 (first entry)
XX
DE Mouse antibody F4-7 light chain variable region coding sequence.
XX
KW Primer; amplification; PCR; mouse; kappa chain; heavy chain; Fab;
KW antibody; immunotolerance; animal; variegated display library;
KW variable region; antigen; immunorecessive; cell surface marker; foetal;
KW cancer; stem cell; variant; therapy; Alzheimer's disease; hybridoma;
KW familial hypercholesterolaemia; binding affinity; ds.
XX
OS Mus musculus.
XX
FH Key Location/Qualifiers
FT CDS 67. .399
FT /*tag= a
FT /product= "antibody F4-7 light chain variable region"
XX
PN WO9515982-A2.
XX
PD 15-JUN-1995.
XX
PF 08-DEC-1994; 94WO-US014106.
XX
PR 08-DEC-1993; 93US-00164022.
PR 06-DEC-1994; 94US-00350400.
XX
PA (GENZ) GENZYME CORP.
XX
PI Barsomian G, Copeland DP, Hillhouse D, Johnson T;
XX
DR WPI; 1995-224291/29.
DR P-PSDB; AAR75459.
XX
PT Generating new antibodies specific for immunorecessive epitopes - by
PT selection from variegated V gene library cloned from immuno:tolerance
PT derived antibody repertoire, useful in diagnosis, purifcn. and therapy,
PT e.g. of cancer.
XX
PS Disclosure; Page 80-81; 109pp; English.
XX
CC The coding sequence of the light chain variable region from the mouse
CC antibody F4-7. This sequence was isolated from a variegated display
CC library (VDL) of variable regions derived from a repertoire of antibodies
CC from an immunotolerised animal. The VDL is generated by PCR amplifying
CC the variable regions from the antibody coding sequences using the primers
CC AAQ74153-74. The variable regions, esp the complementarity determining
CC regions (CDR; see AAR75462-93 for examples of CDRs) from the
CC immunotolerant animals' antibodies are used to construct an antibody
CC against a immunorecessive antigen e.g. a cell surface marker on a foetal,
CC cancer or stem cell, which can differentiate between variant or related
CC forms of the antigen. The antibodies generated can be used in the
CC diagnosis, e.g. detection of the immunorecessive antigen, or in therapy
CC e.g. of cancer, Alzheimer's disease or familial hypercholesterolaemia.
CC The method of production of the antibody allows rapid and sensitive
CC isolation of antibodies that would be difficult to isolate by standard
CC methods. The antibodies produced have greater binding affinity than those

Exhibit 2
2 of 2

CC produced by combinatorial/hybridoma methods
XX
SQ Sequence 723 BP; 205 A; 195 C; 172 G; 151 T; 0 U; 0 Other;

Query Match 90.2%; Score 335.4; DB 2; Length 723;
Best Local Similarity 95.6%; Pred. No. 6.1e-93;
Matches 345; Conservative 0; Mismatches 16; Indels 0; Gaps 0;

```
Qy          6 CGATATTGTGATGACACAATCTACAGCTTCCTTAGCTGTATCTCTGGGGCAGAGGGCCAC 65
              ||| |||||||||||| || ||| | ||||||||||||||||||||||||||||||||||
Db         66 CGACATTGTGATGACCCAGTCTCCTGCTTCCTTAGCTGTATCTCTGGGGCAGAGGGCCAC 125

Qy         66 CATCTCATGCAGGGCCAGCCAAAGTGTCAGTACATCTAGCTATAGTTATATGCACTGGTA 125
              ||||||||||||||| ||| |||||||||||||||||||| ||||||||||||||||||
Db        126 CATCTCATGCAGGGTCAGGCAAAGTGTCAGTACATCTAGCCATAGTTATATGCACTGGTA 185

Qy        126 CCAACAGAAACCAGGACAGCCACCCAAACTCCTCATCAAGTATGCATCCAACCTAGAATC 185
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        186 CCAACAGAAACCAGGACAGCCACCCAAACTCCTCATCAAGTATGCATCCAACCTAGAATC 245

Qy        186 TGGGGTCCCTGCCAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACCCTCAACATCCA 245
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        246 TGGGGTCCCTGCCAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACCCTCAACATCCA 305

Qy        246 TCCTGTGGAGGAGGAGGATACTGCAACATATTACTGTCAGCACAGTTGGGAGATTCCGCT 305
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        306 TCCTGTGGAGGAGGAGGATACTGCAACATATTACTGTCAGCACAGTTGGGAGATTCCGTA 365

Qy        306 CACGTTCGGTGCTGGGACCAAGCTGGAGCTGAAACGGGCTGATGCTGCACCAACTGTATC 365
              ||||||||| |  |||||||||||||  | ||||||||||||||||||||||||||||||
Db        366 CACGTTCGGAGGGGGGACCAAGCTGGAAATAAAACGGGCTGATGCTGCACCAACTGTATC 425

Qy        366 C 366
              |
Db        426 C 426
```